IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	)	C.A. No. 23-975-RGA-SRF

DEFENDANT'S FINDINGS OF FACT RELATED TO INVALIDITY OF U.S. PATENT NO. 11,826,327

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TABLE OF ABBREVIATIONS

Asserted Patents & Parties

'327 patent or '327	U.S. Patent No. 11,826,327
Asserted Claims	Claims 1, 5, 6, 9, 14, 17 of U.S. Patent No. 11,826,327
Liquidia or Defendant	Liquidia Technologies, Inc.
UTC or Plaintiff	United Therapeutics Corporation

Commonly Used Terms & Abbreviations

'793 patent	U.S. Patent No. 10,716,793 (DTX2)
'507 patent	U.S. Patent No. 9,339,507 (DTX62)
2018 Earnings Call	United Therapeutics Corporation FQ1 2018 Earnings Call Transcript, (May 2, 2018) (DTX3)
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
Agarwal	M. Agarwal and A.B. Waxman, *Inhaled Treprostinil in Group-3 Pulmonary Hypertension*, J. Heart and Lung Transplant. 34(4):S343 (2015) (DTX161)
BNP	B-type natriuretic peptide
CPFE	Combined pulmonary fibrosis and emphysema
DPI	Dry powder inhaler
Dr. Channick	Richard Channick, M.D.
Dr. Hill	Nicholas Hill, M.D.
Dr. Nathan	Steven Nathan, M.D.
Dr. Saggar	Rajan Saggar, M.D.
Dr. Tapson	Victor Tapson, M.D.
Dr. Thisted	Ronald Thisted, Ph.D.
Dr. Waxman	Aaron Waxman, M.D.
Dr. Wertheim	Bradley Wertheim, M.D.
Faria-Urbina	M. Faria-Urbina, et al., *Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease*, Lung 196:139–146 (2018) (DTX348) (Supplementary Materials at DTX505)
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
FOF	Findings of Fact related to Invalidity of U.S. Patent No. 11,826,327
HRCT	High-resolution computed tomography
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
INCREASE	A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of

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	Inhaled Treprostinil in Subjects With Pulmonary Hypertension Due to Parenchymal Lung Disease
IPF	Idiopathic pulmonary fibrosis
IPR	*Inter partes review*
iTre	Inhaled treprostinil
ITT population	Intent-to-treat population (ie all patients in INCREASE)
IV	Intravenous
Mcgs	Micrograms
mPAP	Mean pulmonary artery pressure
NDA	New Drug Application
NEJM Paper	A. Waxman, et al., *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease*, N. Eng. J. Med. 384(4):325 (2021) (DTX363)
NT-proBNP	N-terminal pro b-type natriuretic peptide
Parikh	Kishan Parikh et al, *Safety and Tolerability of High-dose Inhaled Treprostinil in Pulmonary Hypertension*, 67 J. Cardiovascular Pharmacology 322-25 (2016) (DTX51)
PAH	Pulmonary arterial hypertension (Group 1 PH)
PAWP	Pulmonary artery wedge pressure
PCWP	Pulmonary capillary wedge pressure
PF	Pulmonary fibrosis
PFT	Pulmonary function test
PH	Pulmonary hypertension
PH-ILD or ILD-PH	Pulmonary hypertension associated with interstitial lung disease (Group 3 PH)
POSA	Person of ordinary skill in the art
PTAB	Patent Trial and Appeal Board
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
Saggar 2014	Saggar, R., et al., *Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis*, Thorax 2014;69:123–129 (2014) (DTX10)
USPTO/PTO	United States Patent and Trademark Office
V/Q	Ventilation/perfusion
WHO	World Health Organization
WU	Wood unit

I. DIAGNOSING PH-ILD

1. PH is elevated blood pressure in the pulmonary artery, and is classified into five WHO groups, including Group 1 PAH and Group 3 PH, which includes PH-ILD. Tr. 76:25-77:2, 77:14-78:10, 171:18-172:9. PH is diagnosed using RHC, which measures pulmonary hemodynamic parameters including mPAP, PVR, and PCWP. Tr. 171:21-172:1, 502:17-22. ILD involves damage to the interstitium, the space between the alveoli and the pulmonary capillaries. Tr. 72:15-73:10, 172:2-9. The ILD component of PH-ILD, is diagnosed using use PFTs, HRCT, and in some cases, lung biopsies. Tr. 81:22-83:17, 171:18-172:9.

2. PH-ILD encompasses a spectrum of severities for both the PH and ILD components. Tr. 434:25-435:18. Dr. Nathan acknowledged PH-ILD included patients with PH ranging from mild to severe. Tr. 130:11-131:17; PTX471, 5. Dr. Nathan's 2019 paper shows patients with chronic lung disease ("CLD") have a range of hemodynamic profiles, highlighting that diagnosing PH-ILD isn't black and white and that patients falling in the intervening "gray zone" are still PH-ILD patients. PTX471, 4-5; Tr. 130:3-132:8, 132:19-133:24. CLD patients with PH have an mPAP of 21-24 mmHg with PVR $\geq$ 3 WU, or an mPAP 25-34 mmHg and CLD patients with severe PH have a mPAP $\geq$ 35 mmHg, but these patients would all be diagnosed with PH-ILD. *Id.* Dr. Channick confirmed the hemodynamic criteria used to define Group 1 and Group 3 PH are the same. Tr. 432:13-433:20. POSAs also testified that patients with "severe" or "out of proportion" PH to their ILD would still be diagnosed with PH-ILD. Tr. 346:20-347:8.

3. Drs. Nathan, Hill, Channick, and Tapson affirmed their confidence in diagnosing PH-ILD. Tr. 81:22-83:17, 617:2-17, 728:12-23, 325:16-23. Dr. Nathan conceded that Drs. Hill, Saggar, Tapson, and Channick could accurately diagnose PH-ILD and his suggestion that Dr. Waxman cannot properly diagnose PH-ILD lacks credibility. Tr. 722:18-723:13.

II. THE ASSERTED CLAIMS ARE INVALID

4. UTC asserts Liquidia infringes claims 1, 5, 6, 9, 14, and 17 of the '327 patent. Tr. 113:6-9. Liquidia stipulated to direct and indirect infringement of claims 1 and 14. Tr. 28:7-10. Liquidia asserts both that it does not infringe claims 5, 6, 9, and 17 of the '327 patent, and that claims 1, 5, 6, 9, 14, and 17 are invalid under §§102, 103, and/or 112.

5. The '327 patent is entitled "Treatment for Interstitial Lung Disease." JTX1. The '327 patent issued on November 28, 2023. The claims are based on INCREASE. Tr. 232:14-1, 436:2-718-23, 629:9-11, 712:3-8. At the time of that study, Tyvaso was already FDA-approved to treat PAH. Tr. 328:25-329:5. INCREASE served as the basis for obtaining FDA's subsequent approval of Tyvaso for the treatment of PH-ILD. Tr. 338:3-25.

6. Independent claim 1 requires a method of treating a patient with pulmonary hypertension associated with interstitial lung disease, which the Court has construed to mean "pulmonary hypertension due, at least in part, to a patient's interstitial lung disease." D.I. 393, 5. Claim 1 does not have a severity requirement for the PH or ILD component. Tr. 134:5-13. INCREASE, which the claims are based on, had a preference for PH-ILD patients with severe PH. Tr. 134:17-20, 326:6-16, 327:1-12. Claim 1 requires an improvement in exercise capacity, which can include, but is not limited to, 6MWD. D.I. 155, 1; Tr. 512:3-10, 138:6-140:137, 187:7-188:11, 222:3-9. Other metrics that indicate improvements in exercise capacity include the three-minute step test, cardiopulmonary exercise testing, functional class, and patient reported outcomes. Tr. 187:12-188:11, 188:17-189:15, 449:9-16, 594:15-595:4.

7. Claims 5, 6, 9, and 17 are directed to the intended results stemming from the method of treatment described in claim 1. JTX1, cls. 5, 6, 9, and 17; Tr. 142:2-6. Claim 14 depends on claim 11, and requires the use of a dry powder inhaler. JTX1, cl. 14.

8. A POSA as of April 17, 2020, would have a medical degree with a specialty in

pulmonology or cardiology, plus at least two years of experience in treating patients with PH as an attending, including PH associated with interstitial lung disease including with inhaled therapies or an equivalent degree of experience. Tr. 431:24-432:9. According to UTC, the POSA would also collaborate with others. Tr. 864:24-865:19, 732:4-9, 895:6-18.

III. CLAIMS 5, 6, 9, AND 17 ARE DIRECTED TO INTENDED RESULTS

9. UTC asserts that to infringe claims 5, 6, 9, and 17, no additional steps need to be performed beyond those necessary to perform claim 1. Dr. Nathan testified that for these claims neither doctors nor patients need to measure NT-proBNP, exacerbations of ILD, FVC, or 6MWD, and no statistical analysis need be performed. Tr. 141:23-142:1, 142:18-24, 144:9-18, 153:8-11. Dr. Nathan testified that a patient need not even achieve the outcomes recited in claims 5, 6, 9 and 17 for direct infringement to occur. Tr. 142:13-17. This is because "the outcomes in Claims 5, 6, 9, and 17 are the intended result of the dosing from Claim 1 in PH-ILD patients." Tr. 142:3-6.

10. According to Dr. Nathan, if a doctor prescribes Yutrepia in accordance with claim 1, claims 5, 6, 9 and 17 are "automatically" infringed. Tr. 142:7-12, 143:8-22. His opinion is based solely on his belief that YUTREPIA infringes based on Tyvaso's performance in INCREASE, and not from any data of YUTREPIA's clinical performance. Tr. 145:5-13.

IV. THE ASSERTED CLAIMS OF THE '327 PATENT ARE INVALID UNDER § 103

A. The '793 Patent Is Prior Art

11. The '793 patent issued on July 21, 2020 from a non-provisional application filed on May 14, 2007. DTX2, 1. The specific application that led to the '793 patent was filed on January 31, 2020. *Id.* The patent identifies Horst Olschewski, Robert Roscigno, Lewis J. Rubin, Thomas Schmehl, Werner Seeger, Carl Sterritt, and Robert Voswinckel as inventors. *Id.* The patent claims priority to provisional application No. 60/800,016, filed May 15, 2006. *Id.*

12. The '327 patent issued on November 28, 2023 from an application filed on April

16, 2021. JTX1, 1. The '327 patent identifies Leigh Peterson, Peter Smith, and Chunqin Deng as inventors. *Id.* The '327 patent claims priority to provisional patent application Nos. 63/011,810 filed on April 17, 2020 and 63/160,611 filed on March 12, 2021. *Id.*

1. The § 102(b)(2)(C) exception does not apply

13. UTC did not offer evidence that any inventor of the '793 or '327 patents was subject to an obligation to assign any rights in either patent prior to April 17, 2020, the claimed effective filing date of the '327 patent. UTC did not offer evidence that any named inventors of the '793 patent were ever employees of UTC, whether those inventors had obligations to assign patent rights to UTC, or when those inventors may have assigned any patent rights to UTC. UTC also did not offer evidence that any named inventor of the '327 patent had any obligation to assign patent rights to UTC or when any of those inventors may have assigned any patent rights to UTC.

14. UTC offered no evidence that the rights in the '793 and '327 patents were commonly owned, let alone owned in their entirety, by UTC on or before April 17, 2020.

15. No inventors of the '793 patent testified at trial. '327 patent inventor Peter Smith testified twice at trial. Chunqin Deng, '327 patent inventor, testified at trial via deposition. Drs. Smith's and Deng's testimony did not address ownership of patents or any obligation to assign patents to UTC. The third inventor, Leigh Peterson, was listed on UTC's witness list as an individual UTC may call live at trial, but she did not testify at trial. D.I. 335 Ex. 6, 2.

16. UTC's patent prosecution counsel, Stephen Maebius, testified at trial via deposition. UTC's VP and associate general counsel of intellectual property, Shaun Snader, testified at trial via deposition. Messrs. Snader's and Maebius's testimony did not address UTC's ownership of patents or any obligation that inventors may have had to assign patents to UTC. Mr. Maebius was on UTC's trial witness list as someone UTC may call live, but he did not testify live. D.I. 335 Ex. 6, 2. Mr. Snader was at counsel table each day of trial, but did not testify live.

2. The '793 patent is applicant admitted prior art

17. The patent specification states that "[p]ulsed inhalation devices are disclosed, for example, in … U.S. Pat. Nos. … 9,339,507… and 10,716,793." JTX1, 20:48-57. Dr. Nathan testified the '793 and '507 patents were incorporated in the '327 patent "in their entirety for the disclosure of dry powder inhalers and dry powder compositions of treprostinil." Tr. 897:6-898:5.

18. UTC and Dr. Nathan admitted that the '793 patent was considered by the examiner during prosecution as part of a "prior art search" conducted by the PTO. D.I. 26, 14 ("there can be no dispute that the '793 patent . . . was before the examiner during prosecution"); D.I. 28 ¶103 (Dr. Nathan stating under oath "[o]n August 21, 2022 a prior art search was performed by the USPTO" and returned results "including the '793 patent[.]"). Dr. Nathan further testified under oath in response to inequitable conduct allegations that materials withheld from the examiner by UTC were "cumulative" to the '793 patent. *Id*. ¶¶220-26.

B. Claim 1 Is Obvious

1. *Faria-Urbina* discloses the limitations of claim 1

19. *Faria-Urbina* is a 2018 peer-reviewed publication with supplementary materials titled "Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease" with lead author Dr. Waxman. DTX348, 1; DTX505; Tr. 444:17-445:12, 620:1-19.

20. *Faria-Urbina* is a study in which 22 patients were diagnosed and prospectively treated with iTre by Dr. Waxman and others at Brigham and Women's Hospital from 2009-2016, with outcomes retrospectively evaluated. DTX348, 1-2; Tr. 388:5-14. Drs. Nathan and Thisted incorrectly claimed the patients were retrospectively diagnosed; only the data analysis was retrospective. Tr. 834:9-25, 733:23-734:9, 755:8-13, 377:8-18, 388:5-14, 450:14-451:23. That *Faria-Urbina* is retrospective does not diminish that it demonstrates real-world experience with the successful treatment of PH-ILD with Tyvaso. Tr. 377:8-18, 388:5-14, 450:14-451:23.

a. *Faria-Urbina* discloses the "method of improving exercise capacity in a patient having PH-ILD"

21. *Faria-Urbina* discloses the claimed treatment of PH-ILD patients. Tr. 452:10-12. Of the 22 Group 3 PH patients, 9 were identified as PH-ILD, and 5 were identified as PH-CPFE—a sub-type of PH-ILD. DTX348, 2-3; Tr. 388:20-389:6, 391:1-13, 452:16-23, 852:9-11. PH-CPFE patients were included in INCREASE and are part of the claimed PH-ILD patients in the '327 patent. Tr. 454:17-22, 478:6-12, 852:9-11. Dr. Waxman confirmed the patient population in *Faria-Urbina* is the same patient population as INCREASE. Tr. 415:7-14.

22. Dr. Nathan contends that the patients in *Faria-Urbina* are more likely PAH patients than PH-ILD patients. Tr. 902:9-13. But this opinion relies on his retrospective re-diagnosis of patients without access to the patients or their records, which is exactly the type of improper analysis he mistakenly criticized Dr. Waxman for undertaking. Tr. 902:14-18, 904:22-905:21. Dr. Waxman diagnosed these patients by reviewing RHC data to diagnose PH and reviewing HRCT to diagnose ILD, which Dr. Nathan testified should be used to make a proper diagnosis. DTX348, 2 (design and study population); Tr. 374:20-375:8, 377:8-18, 835:3-836:6, 838:18-839:15, 902:19-903:9. Dr. Nathan's doubt about Dr. Waxman's ability to diagnose PH-ILD lacks credibility.

23. Dr. Nathan also opines that the baseline hemodynamics of patients in *Faria-Urbina* are more severe than the patients in INCREASE. Tr. 842:15-20. For example, Dr. Nathan emphatically stated that he had never seen "an ILD-PH patient alive with a PVR of 15.2." Tr. 847:8-848:6. Yet, he directly contradicted himself by acknowledging that PH-ILD patients in INCREASE had even more severe hemodynamic profiles, including patients with a PVR of 18.05. Tr. 905:25-908:5. Notably, Dr. Nathan confirmed he personally reviewed patient data in INCREASE to "make sure we were enrolling the right patient population." Tr. 837:4-8. Nonetheless, hemodynamic values for the *Faria-Urbina* patients fall within the range of the

hemodynamic profiles in Dr. Nathan's 2019 paper (*see* FOF2), INCREASE, and the patients encompassed by the '327 patent claims. Tr. 906:21-908:1, 436:8-437:24; JTX1, 41-42 (Table 7).

24. *Faria-Urbina* discloses improvements in exercise capacity in PH-ILD patients treated with Tyvaso, including improvements in 6MWD. Tr. 453:4-455:1. Tables S3 and S4 report increases in 6MWD of 21 and 55 meters for PH-ILD and PH-CPFE patients, respectively, from baseline to follow-up. DTX505, 3-4; Tr. 453:17-454:16, 477:24-478:12, 681:19-682:3.

b. *Faria-Urbina* discloses the claimed effective dosing amount

25. The PH patients in *Faria-Urbina* were treated with iTre and followed for at least three months. DTX348, 2 (treatment regimen and follow-up); Tr. 450:7-13. A POSA would understand that the iTre used was Tyvaso, the only iTre available at the time. Tr. 455:9-19, 389:17-390:6. *Faria-Urbina* dosed iTre as follows: "three breaths (18μg) four times daily (72 μg/day)" which were "increased as tolerated . . . to achieve a dose of at least 9-12 breaths or more (≥54μg) four times daily (≥216μg/day)." DTX348, 2.

26. Dr. Nathan admitted that Tyvaso dosing in *Faria-Urbina* is the same as the claimed dosing. Tr. 901:17-902:8, 456:5-8, 476:6-18, 631:12-632:2. A POSA would understand that *Faria-Urbina* describes administering 6μg treprostinil per breath, as required in claim 1. DTX348, 2 (treatment regimen and follow-up); Tr. 389:17-22. A POSA would also understand that *Faria-Urbina*'s description of "increas[ing] as tolerated . . . to achieve a dose of at least 9-12 breaths or more (≥54μg) four times daily (≥216μg/day)" describes the same range provided in claim 1 of "at least 15 micrograms up to a maximum tolerated dose" in a single administration event. DTX348, 2 (treatments and methods); Tr. 455:20-456:8, 390:7-16. This dosing was used because it was the usual Tyvaso dosing for Group 1 PAH. Tr. 389:17-390:6.

27. Dr. Nathan's opinion that peer-reviewed *Faria-Urbina* is "garbage" that no rational POSA would rely on lacks credibility given UTC's admissions that this work by Dr. Waxman

provided the rationale for INCREASE . Tr. 920:24-921:19, 853:10-24, 401:22-403:1; FOF21, 55. His opinion that *Faria-Urbina* is "hypothesis-generating at best" is unconvincing given he also called the FVC results from INCREASE "hypothesis-generating," and UTC obtained patent claims based on this data (cls. 9 and 10). *See* Tr. 853:10-24, 857:12-20, 926:18-927:7, 629:18-630:2; DTX9, 9. Regardless, even hypothesis-generating results still provide a POSA with motivation and reasonable expectation of success. FOF132.

2. The '793 patent discloses the limitations of claim 1

28. The '793 patent, titled "Treprostinil Administration by Inhalation," issued on July 21, 2020 from Application No. 16/778,662, filed on January 31, 2020. DTX2, 1. It claims priority to provisional application No. 60/800,016 filed May 15, 2006, Application No. 11/748,205, filed May 14, 2007 (the "'205 application"), and other applications dated from 2009-2019. DTX2, 1:6-16; Tr. 456:9-23, 458:4-9. The '205 application is the first non-provisional application filed in the family and its specification is the same as the '793 patent specification. Tr. 456:9-458:9.

29. Claim 1 of the '327 patent is directed to:

> A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath. JTX1, 50.

a. The '793 patent discloses a "method of improving exercise capacity in a patient having PH-ILD"

30. The '793 patent discloses a method of treating PH-ILD patients. Tr. 458:11-23. Example 2 of the patent describes three different studies of iTre in a total of 123 patients. DTX2, 12:20-27. Table 3 states that the "[e]tiology of pulmonary hypertension" of patients in the study included patients with "pulmonary fibrosis (f)," which a POSA would understand is a form of PH-ILD. DTX2, 23 (Table 3); Tr. 458:11-23. The patent also discloses a method of treating PH-ILD

patients because it discloses a method of treating all PH patients, including PH-ILD, with iTre. DTX2, 18:21-31 (cl. 1), 2:66-3:21, 5:27-36; Tr. 458:24-459:2, 859:14-17. This Court has already determined that the method of treatment in the patent includes all 5 groups of PH, including, PH-ILD (Group 3 PH). Trial Op., 38-39, 41, *UTC v. Liquidia*, No. 20-755-RGA (D. Del. Aug. 31, 2022), D.I. 433; Tr. 458:24-459:21, 463:5-13.

31. UTC admitted to the USPTO and the FDA that the '793 patent covers Tyvaso's approval for improving exercise capacity in PH-ILD patients, confirming a POSA's belief that the '793 patent describes the use of iTre to improve exercise capacity in PH-ILD patients. Tr. 460:12-15, 428:14-430:19, 724:8-13, 728:24-729:6; DTX28, 6; *see also* Tr. 463:5-13. Citing the 2021 Tyvaso label in its Patent Owner Response for the '793 IPR, UTC admitted that "[t]he claimed invention of the '793 patent satisfies a long-felt unmet need in the treatment of pulmonary hypertension" including the treatment of PH-ILD patients. DTX7, 61; Tr. 424:12-425:14, 459:24-460:15. Mr. Maebius, UTC's lead IPR counsel, testified this meant the '793 patent covers Tyvaso's PH-ILD indication. Tr. 425:10-426:1. UTC told the FDA on February 12, 2024, that the '793 patent covers Tyvaso's PH-ILD indication. DTX28, 6; Tr. 428:14-430:19. UTC asserted the '793 patent against Liquidia when PH-ILD was added to the Yutrepia label. *See* D.I. 1, ¶4.

b. The '793 patent discloses the claimed effective amount dosing

32. The '793 patent also discloses the effective amount dosing of iTre of claim 1. Examples 1 and 2 of the '793 patent disclose using iTre. DTX2, 20-23; Tr. 460:16-461:18. The '793 patent states iTre is administered "from about 15 µg to about 100 µg" (DTX2, 7:55-59) in "20 breaths or less" and preferably in 3, 2, or 1 breaths. *Id.*, 7:60-67. A POSA would understand that this dosing overlaps with the dosing in the '327 patent, claim 1. Tr. 461:9-18.

33. A POSA would therefore understand that the combination of *Faria-Urbina* and the '793 patent disclose all the limitations of claim 1. Tr. 461:15-18, 449:24-450:2.

3. A POSA would be motivated to combine *Faria-Urbina* and the '793 patent with a reasonable expectation of success

34. A POSA would be motivated to combine *Faria-Urbina* and the '793 patent because they are directed to the same subject matter—the use of the same drug (treprostinil) delivered via the same route (inhaled) to treat PH-ILD patients. Tr. 447:18-22. Moreover, in *Faria-Urbina*, the dosing for treating PH-ILD patients was based on the standard Tyvaso dosing used for PAH because this was the dosing doctors were familiar with. Tr. 389:17-390:3. This same dosing was used in INCREASE, and ultimately claimed in the '327 patent, because the steering committee had experience with that approach in both PAH and PH-ILD patients and there was no reason to change. Tr. 338:18-339:16, 403:2-404:13, 405:20-23, 411:23-413:16; DTX357; DTX360. Since the '793 patent discloses overlapping dosing, a POSA would be motivated to combine the '793 patent with *Faria-Urbina*. DTX348, 2 (Treatment regimen and follow-up); DTX2, 7:55-64, 18:21-31 (cl. 1); Tr. 447:7-17.

35. These references also provide a reasonable expectation of success with respect to claim 1. *Faria-Urbina* reports significant improvements in 6MWD for PH-ILD patients after receiving Tyvaso, demonstrating improved exercise capacity with no mention of safety concerns. DTX348, 5 (Table 2); Tr. 138:6-11, 187:12-188:11. And UTC admitted that the '793 patent covers improving exercise capacity in PH-ILD patients. FOF31. Thus, a POSA would have a motivation to combine *Faria-Urbina* with the '793 patent and have a reasonable expectation of successfully improving exercise capacity in PH-ILD patients.

4. Additional proof of motivation with a reasonable expectation of success

a. Decade-long successful off-label use of Tyvaso in PH-ILD

36. POSAs were treating PH-ILD patients with Tyvaso soon after its approval for PAH in 2009. FOF117-122. These POSAs, working independently at various medical centers,

including Drs. Waxman, Tapson, Channick, Hill, and Rajeev and Rajan Saggar, followed the dosing on the Tyvaso label for PAH and in many cases safely titrated up to doses of 12 breaths or higher. *Id.* These doctors reported improvements in PH-ILD patients' exercise capacity and other subjective improvements. *See* DTX161; DTX348; FOF119-120. This off-label use provides proof that doctors were motivated and actually achieved success in improving exercise capacity in PH-ILD patients using Tyvaso according to the claimed dosing. Tr. 461:25-462:19. Their off-label use of Tyvaso in PH-ILD following its approval in PAH is not surprising because once a drug works in WHO Group 1 PAH, it makes sense to try it in other WHO Groups because both are treated using vasodilation, which is the mechanism of action for treprostinil. Tr. 229:21-230:19, 462:20-463:4, 257:9-17, 333:16-22, 381:21-386:18, 415:7-416:4, 439:16-440:1.

37. Any suggestion by Dr. Nathan that these reported off-label PH-ILD patients were actually on-label PAH patients is not credible because it directly contradicts the testimony of Drs. Waxman, Tapson, Channick, Hill, and Saggar. FOF119-121.

b. The prior art corroborates the successful off-label use

38. The successful off-label use of Tyvaso in PH-ILD patients is corroborated by contemporaneous reports in the prior art, including *Agarwal*, *Parikh*, and Dr. Waxman's public John Vane presentation, which all confirm the actual treatment of PH-ILD patients with Tyvaso and support a motivation and reasonable expectation of success with respect to claim 1. POSAs and UTC were aware of these publications as of April 2020. Dr. Rajeev Saggar testified he was aware of multiple papers he believed demonstrate that Tyvaso had been used to safely treat PH-ILD, including *Agarwal*, *Parikh*, and *Faria-Urbina* prior to 2020. Tr. 64:14-65:17. Peter Smith, a named inventor, testified that *Agarwal* reflected UTC's knowledge of off-label use of Tyvaso in PH-ILD patients. Tr. 239:15-240:19. And Dr. Rothblatt provided public remarks on data and publications in PH-ILD patients. DTX3, 10; FOF57.

39. ***Agarwal*** is an abstract titled "Inhaled Treprostinil in Group-3 Pulmonary Hypertension," published in April 2015 and publicly presented at the International Society of Heart and Lung Transplantation meeting in 2015. DTX161, 8 (abstract); Tr. 367:8-25, 372:4-15. The lead author is Dr. Waxman. DTX161, 8.

40. *Agarwal* describes prospectively treating 35 WHO Group-3 PH patients, including 20 patients with PH-ILD (15 patients with restrictive disease and 5 patients with mixed obstructive/restrictive disease). DTX161, 8; Tr. 463:14-464:2, 464:17-23. The patients in *Agarwal* received 3 breaths of Tyvaso 4 times daily and increased to 9-12 breaths 4 times daily, as tolerated, like claim 1. DTX161, 8; Tr. 464:11-16, 464:24-465:3. *Agarwal* reports the patients showed subjective improvement, and that patients with restrictive disease, i.e., PH-ILD, showed improvements in exercise capacity following treatment with a greater median improvement in 6MWD (61m) than the overall patient group (45m, $p = 0.0019$). *Id.* *Agarwal* concluded that "Group-3 PH can be effectively and safely treated" with iTre. DTX161, 8.

41. On October 21, 2014, Dr. Waxman sent the *Agarwal* abstract to Dr. Gil Golden at UTC to "convince [UTC] to do a clinical trial," further evaluating iTre for the treatment of Group 3 patients, including PH-ILD patients. DTX287, 3; Tr. 368:9-369:8. Dr. Golden responded "he loved it." DTX287, 2; Tr. 370:7-25. Dr. Rajan Saggar testified that the work disclosed in *Agarwal* (and in *Faria-Urbina*) encouraged the use of iTre for the treatment of PH-ILD. Tr. 299:23-300:24. Dr. Smith testified that Dr. Waxman's work in *Agarwal* was the conception of the idea for the INCREASE study. Tr. 235:14-23. In view of this testimony, Dr. Nathan's opinion that "no rational POSA would rely on" *Agarwal* is not credible. Tr. 921:2-11. *Agarwal* further motivates a POSA, with a reasonable expectation of success, to achieve claim 1 of the '327 patent.

42. ***Parikh*** is a 2016 peer-reviewed article titled "Safety and Tolerability of High-dose

Inhaled Treprostinil in Pulmonary Hypertension," with lead author Dr. Tapson, published in the Journal of Cardiovascular Pharmacology. DTX51, 1; Tr. 341:7-342:6, 343:3-7, 465:21-25.

43. *Parikh* is a retrospective study of 80 PH patients at the Duke University Medical Center PH Clinic who were treated with iTre. DTX51, 1 (abstract); Tr. 466:4-9. Of these patients, 25 were categorized as having Group 3 PH, 6 of which had PH-ILD and 6 with CPFE (mixed pattern). DTX51, 3 (Table 1); Tr. 343:21-344:21, 466:10-19.

44. The patients in *Parikh* were administered Tyvaso prior to August 2012. DTX51, 2; Tr. 466:20-467:5. The initial dose started at three breaths per session, with 6 mcgs per breath and titrated up to 12 breaths, amounting to 72 mcgs total, like *Faria-Urbina* and claim 1. DTX51, 2-3; Tr. 344:22-345:12, 467:12-17. Dr. Tapson testified this dosing aligned with the dosing in INCREASE and confirmed that he and his colleagues used this dosing when treating PH-ILD patients off-label with Tyvaso. Tr. 345:13-23. *Parikh* was funded by UTC and reflects UTC's knowledge of off-label use of Tyvaso in PH-ILD patients. Tr. 238:9-240:13; DTX51, 1.

45. *Parikh* reported increases in 6MWD after treatment. DTX51, 3; Tr. 467:18-468:4. Additionally, NT-proBNP decreased by 630 ng/L following treatment. DTX51, 3; Tr. 468:13-19. *Parikh* concluded that high doses of iTre were well-tolerated, noting there was a "favorable safety and tolerability profile among PH WHO group 3 patients in [the] study for whom there are currently no approved therapies, and [iTre] may provide benefit in this patient population." DTX51, 4. *Parikh* further motivates a POSA, with a reasonable expectation of success, to achieve claim 1 of the '327 patent.

46. **Dr. Waxman's March 17, 2017 Presentation** titled "Is There a Therapeutic Opportunity for Prostacyclins in Patients with PH Secondary to Primary Pulmonary Disease" at the 12th Annual John Vane Memorial Symposium, discussed the use of prostacyclin in patients

with Group 3 PH, including PH-ILD. DTX140; Tr. 382:5-23. Dr. Waxman confirmed the data he discussed during his presentation was the same data described in *Faria-Urbina*. Tr. 387:4-18.

47. Dr. Waxman discussed the rationale for using iTre in PH-ILD patients, including that "treatment directed at pulmonary vascular remodeling should potentially benefit any patient with a form of pulmonary vascular disease" and that "pathways that are active in patients with PAH are also active in patients with Group 3 and even Group 2 and Group 4 and even Group 5 [PH]." DTX140, 3:4-7, 3:20-22. He confirmed that his opinion was, regardless of any associated diseases, "if a patient develops pulmonary vascular disease and pulmonary hypertension, there's overlap of the mechanism driving the disease. And if we have a drug that works in one form, we should be able to repurpose it to another." Tr. 382:5-23, 372:16-374:15, 392:4-10, 397:5-25. Dr. Deng provided similar testimony. Tr. 229:19-230:19. He explained that systemic vasodilators distribute the drug throughout the lungs by following blood flow, dilating the lung indiscriminately. *See* Tr. 372:16-374:15. In contrast, iTre is delivered only to well-ventilated areas of the lung, selectively vasodilating areas where it is actually delivered, thereby minimizing the risk of V/Q mismatch. *Id.* Dr. Waxman's presentation further motivates a POSA, with a reasonable expectation of success, to achieve claim 1 of the '327 patent.

c. *Faria-Urbina* and other prior art provided the motivation and expectation of success for INCREASE

48. UTC's own documents confirm that Dr. Waxman's use of Tyvaso for the treatment of PH-ILD was the motivation and proof of concept for INCREASE and the Asserted Claims. None of the inventors on the '327 patent were responsible for the idea of using Tyvaso in PH-ILD patients, named inventors Smith and Peterson had no involvement in developing the INCREASE protocol, and inventor Deng offered no testimony as to his involvement in INCREASE. Tr. 235:14-23, 236:12-18, 244:18-245:5, 691:1-10.

49. **2015 Proof-of-Concept Presentation:** UTC's March 9, 2015 presentation titled "Tyvaso and WHO Group 3, Proof of Concept Review" characterized Dr. Waxman's work reported in *Agarwal* as the "pilot study provid[ing] preliminary evidence supporting the treatment of pre-capillary PAH in patients with advanced lung disease." DTX385, 29; Tr. 241:11-21, 242:4-15, 243:16-244:3, 311:18-312:14, 312:18-313:3. Dr. Waxman testified that he gave the 2015 presentation to convince UTC to run a Phase 3 clinical trial of Tyvaso in PH-ILD patients. Tr. 398:12-399:16. Afterward, UTC president, Roger Jeffs, told Dr. Waxman UTC was going to do the study. Tr. 400:5-20. UTC recognized *Agarwal* was "pilot data" that provided "proof of concept" to fund a clinical trial to obtain FDA approval—the type of information Dr. Nathan said was needed. Tr. 884:11-17.

50. Indeed, the idea of treating PH-ILD patients with iTre came from third-party doctors, not UTC. Dr. Waxman testified that at Brigham's it was his idea. Tr. 375:18-25. Dr. Rajan Saggar testified that doctors at UCLA, not UTC, came up with the idea of using treprostinil in PH-ILD. Tr. 284:12-285:9. For example, on June 8, 2017, Dr. Rajan Saggar contacted UTC with slides for a proposed clinical trial. DTX398, 1; Tr. 57:18-58:12. Dr. Saggar asked that the information not be shared with persons affiliated with INCREASE as they were his own ideas regarding the use of treprostinil in Group 3 PH patients and had been discussing the subject with UTC for over a decade. DTX398, 1; Tr. 58:13-19. Dr. Rajeev Saggar testified that he discussed studying iTre in PH-ILD patients with UTC between 2010 and 2016—long before INCREASE—and that his group at UCLA shared their data with Dr. Rothblatt in the discussions. Tr. 259:25-260:25. Dr. Rajan Saggar testified he was trying to "showcase that treprostinil clearly works very well in this population, even back as early as 2014." Tr. 58:25-59:9.

51. **2017 INCREASE Recruitment Presentation:** Another UTC presentation titled

"Tyvaso in Pulmonary Hypertension Due to Interstitial Lung Disease (PH-ILD): The INCREASE Study" was provided to the INCREASE steering committee members in 2017 to share with other doctors on a non-confidential basis. DTX384; DTX383; Tr. 247:17-248:10, 248:19-25, 249:4-12, 409:24-410:16. The presentation was emailed on November 7, 2017 by Dr. Smith to Drs. Waxman, Nathan, and Tapson. DTX383; Tr. 248:11-18. The slides characterize *Agarwal* as "Supportive Evidence for Tyvaso in WHO Group 3 PH," discuss Dr. Waxman's data from *Agarwal*, and the "Discussion and Conclusion" slide states that "this study provides preliminary evidence supporting the safety and efficacy of inhaled treprostinil in the treatment of Group 3 PH with advanced lung disease complicated by pulmonary vascular remodeling." DTX384, 4, 7; Tr. 249:13-22, 246:6-247:16, 410:17-411:7.

52. **FDA Orphan Drug Letter:** In a November 15, 2017 letter to the FDA supporting UTC's Orphan Drug Designation application, Dr. Waxman stated that "as we have seen in our preliminary studies, it is ***anticipated*** that patients with ILD-PH may be more likely to benefit from prostacyclin therapy such as treprostinil." DTX281, 2 (emphasis added); Tr. 408:2-409:12. His statement cited to *Saggar 2014* and *Agarwal*. DTX281, 2; Tr. 409:13-19.

53. **UTC's Final INCREASE Protocol:** The INCREASE protocol includes a section titled "Rationale For Development of Study Drug in Disease/Condition." DTX373, 18; DTX401, 18-19. This section states "[i]nhaled treprostinil is expected to directly target the more ventilated portion of the lungs in patients with WHO Group 3 PH minimizing the risk of ventilation perfusion mismatch and allowing for improvements in exercise capacity." *Id*. The protocol cites *Agarwal* as rationale for conducting the study. DTX373, 18; DTX401, 18-19; Tr. 401:22-403:1.

54. **INCREASE Investigator's Brochure:** The August 26, 2016, Investigator's Brochure for INCREASE also identified *Agarwal* and *Saggar 2014* as the rationale for treating

patients with PH-ILD with iTre. DTX387, 131, 132; Tr. 39:24-41:18. The Investigator's Brochure would have been submitted to the FDA and provided to investigators in the study. Tr. 40:4-10.

55. **NEJM Paper:** The results of INCREASE were published in the 2021 NEJM Paper. DTX363, 1; Tr. 470:15-17. The NEJM Paper identifies *Faria-Urbina* and *Agarwal* as "pilot studies" that provided a reasonable expectation of success to conduct INCREASE. DTX363, 2; Tr. 406:22-408:1, 470:18-471:15. UTC thus acknowledged the prior art not only provided a motivation to use iTre to treat PH-ILD, but also a reasonable expectation of success.

56. According to Dr. Nathan, given the expense involved, no pharmaceutical company would undertake a Phase 3 clinical trial like INCREASE without proof-of-concept pilot studies to support the trial's success. Tr. 883:8-884:17. UTC's own documents confirm that the prior art studies by Drs. Waxman and Saggar were the pilot studies that provided the proof of concept leading to the motivation and expectation of success in conducting INCREASE.

57. **UTC 2018 Earnings Call:** Public statements made by UTC's CEO, Dr. Rothblatt, during UTC's May 2, 2018 earnings call also motivate a POSA with a reasonable expectation of success for claim 1. DTX3; Tr. 468:20-469:16; FOF127. In response to a question regarding the rationale behind using Tyvaso in PH-ILD, Dr. Rothblatt responded that she was aware that Dr. Waxman, and other doctors, used Tyvaso off-label to treat PH-ILD patients and they told UTC that "this drug works" even better in Group 3 PH than in PAH and specifically in improving exercise capacity. DTX3, 9-10; Tr. 469:17-470:4. Moreover, Dr. Rothblatt responded that she had seen "posters" and "publications" reflecting this successful off-label use and that these data enabled UTC to "power" the INCREASE study. DTX3, 10; Tr. 677:22-678:8. Mr. Bunce, a corporate witness for UTC, confirmed that the factual basis for Dr. Rothblatt's statements was data presented by Dr. Waxman. Tr. 420:13-421:14, 421:19-422:14. Dr. Rothblatt's statements

acknowledge that UTC recognized that Tyvaso was being successfully used off-label for treatment of PH-ILD and improvements in exercise capacity. DTX3, 10; Tr. 470:5-9.

58. In light of the prior art and the experience of a POSA, a POSA would have been motivated with a reasonable expectation of success of achieving claim 1. Tr. 471:20-472:3.

5. The "failed" studies do not negate reasonable expectation of success

59. Dr. Nathan relied extensively on the allegedly "seven deadly studies" to support a lack of motivation, a lack of a reasonable expectation of success, and the idea that the claimed invention was unexpected. Tr. 712:9-714:9, 827:7-828:4. These studies are irrelevant and would not have impacted a POSA's motivation or reasonable expectation of success because none involved the use of treprostinil, let alone iTre, in PH-ILD patients prior to April 2020. Tr. 726:24-727:15. Dr. Nathan acknowledged the irrelevance of these studies, admitting that none of them (except PERFECT) used treprostinil and that he offered no testimony on any failed treprostinil study in PH-ILD. Tr. 720:3-11. He also admitted that none of the drugs, other than iloprost in the ACTIVE trial, were delivered through inhalation but were instead delivered orally. Tr. 720:12-20. Dr. Smith confirmed that he was not aware of a single study evaluating iTre in PH-ILD patients that was negative or inconclusive. Tr. 244:4-7. And Dr. Channick confirmed that all of the "failed" studies used different drugs, and with the exception of the ACTIVE study, were not even looking at prostacyclins or inhaled therapies. Tr. 726:24-727:15.

60. Drs. Channick, Hill, Tapson, Waxman and Saggar all continued their off-label use of Tyvaso in PH-ILD patients even with these "failed" studies. Tr. 332:3-9, 333:10-15, 356:24-357:3, 394:3-21, 255:12-258:17, 595:18-597:20, 599:5-600:10, 727:16-728:2.

61. The ACTIVE study, which Dr. Nathan identified as most similar to INCREASE, used iloprost and Dr. Channick explained that it was not a failed study. Tr. 441:22-445:5. Dr. Nathan admitted that iloprost is a different molecule than treprostinil, with a different half-life and

different pharmacokinetic properties, and requires more frequent administration. Tr. 901:3-16.

62. Dr. Nathan admitted that the PERFECT study was not discontinued until after April 2020, and therefore a POSA would not have been aware of the discontinuation in April 2020. Tr. 126:3-9. Dr. Waxman testified that the PERFECT study was shut down because enrollment was slow, and that he still uses Tyvaso to treat PH-COPD patients (the patient population in PERFECT) because "[i]t works." Tr. 406:2-15.

63. As lead of the RISE-IIP trial, Dr. Nathan was arguably personally impacted by its termination, but Dr. Waxman testified that the RISE-IIP study termination in no way discouraged his continued use of Tyvaso to treat PH-ILD patients because: "[i]t's a different class of drug with different administration, different types of side-effects." Tr. 831:2-22, 394:3-21.

64. Both Drs. Rajan Saggar and Waxman testified that any "failure" of these studies was likely due to due to poor study conduct and/or design. *See* DTX140, 7:3-8:8; Tr. 383:13-25, 261:4-262:2. Thus, these alleged "failures" of different drugs do not detract from a POSA's reasonable expectation of success.

65. Finally, Dr. Nathan's testimony regarding the "failed" studies is not credible as it directly contradicts his rationale why no POSA would rely on *Saggar 2014*. Tr. 854:25-855:20. He opines that a POSA would rely on the "failed" studies (which didn't use treprostinil) because:

> ***all of these drugs work the same. . . no matter how you give them***, inhaled, oral, IV, sub-Q, they all dilate the pulmonary vasculature. . . . [T]o me, it doesn't really matter which drug or how. ***It's the final pathway of dilating the vasculature that's most important, and they all shared that in common***. Tr. 831:23-832:15 (emphasis added).

But with respect to *Saggar 2014*, which actually used treprostinil in PH-ILD patients, Dr. Nathan takes the opposite position, arguing no POSA would rely on it regarding the use of iTre in PH-ILD because it is "a different formulation of a drug given in a different way." Tr. 862:10-20. Dr. Nathan's contradictory testimony weighs against his credibility.

66. Dr. Nathan testified that "only a randomized, controlled clinical trial would provide sufficient proof for a POSA to have a reasonable expectation of success with respect to the [Asserted Claims]." Tr. 923:7-924:20. Dr. Nathan admitted, that in his opinion, nothing but the actual INCREASE results could provide a reasonable expectation of success. Tr. 924:13-17. But none of the claims require a large clinical study, nor do they require the need for FDA approval of iTre in PH-ILD. Further, Dr. Nathan's position is contradicted by UTC's CEO, Dr. Rothblatt, who, in 2018, years before INCREASE results were published, stated "[t]his drug works." DTX3, 10; Tr. 469:17-470:4. Regardless, a POSA does not need the results of a Phase 3 trial to achieve the claimed invention, as a POSA can still reasonably expect the claimed results even if they do not yet know those results with absolute certainty. Tr. 493:3-18, 624:8-16.

C. Claim 17 Is Obvious

67. Claim 17 additionally requires an increase in 6MWD "by at least 10 m after 8 weeks of the administering." JTX1, 51 (cl. 17); Tr. 472:23-473:2. Tables S3 and S4 of *Faria-Urbina* report increases in 6MWD of 21 and 55 meters respectively (greater than at least 10 meters) in PH-ILD patients. DTX505, 3-4; Tr. 477:24-478:12. These patients were followed "for at least 3 months" which is after 8 weeks as required by claim 17. DTX348, 1; 450:7-13. This disclosure in *Faria-Urbina* renders the additional limitation of claim 17 obvious. Tr. 472:18-473:10, 473:18-23. A POSA would be motivated with a reasonable expectation of success for the reasons discussed for claim 1. Tr. 472:6-17, 473:24-474:9.

D. Claim 14 Is Obvious

68. Claim 14 depends on claim 11, which requires "[t]he method of claim 1, wherein said administering is performed by a pulsed inhalation device." JTX1, 50 (cl. 11); Tr. 474:12-21. Claim 14 additionally requires the "pulsed inhalation device is a dry powder inhaler comprising treprostinil or a pharmaceutically acceptable salt thereof." JTX1, 50 (cl. 14); Tr. 474:22-24. Under

the Court's claim construction, a "pulsed inhalation device" "provides for non-continuous inhaled drug delivery," which includes a DPI. D.I. 155, 1; Tr. 474:25-475:9.

69. The '793 patent describes liquid and dry powder formulations of treprostinil. DTX2, 7:22-26, 7:42-54. It also describes inhalation devices for administering iTre including a DPI. DTX2, 7:22-26, 18:36-37 (cl. 4); Tr. 475:7-15.

70. Dr. Nathan acknowledged that the '327 patent specification identifies prior art treprostinil dry powder formulations and treprostinil DPIs. JTX1, 15:1-10, 20:48-57, 21:6-14; Tr. 894:13-895:2. This admitted prior art disclosing making and using treprostinil dry powders and DPIs includes WO2019/237028, the '507 patent, and the '793 patent. JTX1, 15:1-10, 20:48-57, 21:6-14; Tr. 894:16-898:15. The '507 patent has the same specification as the '793 patent and issued on May 17, 2016. DTX62, 1; Tr. 456:9-458:9, 898:8-15. Therefore, even without the '793 patent, claim 14 would be obvious in view of *Faria-Urbina* and '327 patent admitted prior art.

71. DPIs were well-known to POSAs for the treatment of airway diseases, including asthma and COPD, and this prior knowledge is considered for obviousness. Tr. 476:13-15. UTC previously admitted that POSAs knew DPIs were available by 2006, almost fifteen years before the filing date of the '327 patent, and that the processes and requirements for developing a dry powder formulation of a drug were well-known and utilized routine manufacturing and analysis techniques. Pl.'s Proposed Findings of Fact on Validity ¶¶142-145, *UTC v. Liquidia*, No. 20-755-RGA (D. Del. June 1, 2022), D.I. 414. UTC further admitted that methods for determining suitable forms of a drug for use in a DPI were well-known by POSAs prior to 2006. *Id.*, ¶149. UTC even had its expert in the prior litigation, Dr. Smyth, develop and prepare a dry powder formulation of treprostinil according to well-known and routine techniques available to POSAs as of 2006, and demonstrate delivery of doses using the DPI in just three weeks. *Id.*, ¶¶153-54.

72. This Court accepted those facts, finding that by 2006 "[n]umerous dry powder ("DPI") devices were available," that "it was common for a POSA to develop a powder blend and then choose an available DPI for delivery of the powder formulation," that UTC's expert, Dr. Symth, prepared treprostinil dry powder formulations "[u]sing well-known and routine techniques," and that "[s]electing a suitable form of treprostinil was routine." *UTC v. Liquidia*, 624 F. Supp. 3d 436, 465 (D. Del. Aug. 31, 2022), *aff'd*, 74 F.4th 1360 (Fed. Cir. 2023). Therefore, even without the '793 patent, claim 14 would be obvious in view of *Faria-Urbina* and the UTC admitted knowledge of a POSA regarding treprostinil dry powder formulations and treprostinil DPIs.

73. Dr. Nathan's argument that a POSA would not be able to formulate a dry powder formulation of treprostinil for use in the DPI ignores that a POSA would work as a member of a team, including drug formulators. Tr. 864:24-865:19, 895:6-17, 732:4-9. UTC's and Dr. Nathan's argument is also foreclosed by UTC's prior argument and this Court's prior ruling that as of 2006 POSAs knew how to make and use dry powder formulations of treprostinil for use in DPIs, including based on the '793 patent specification, precluding UTC from asserting claim 14 is non-obvious. *UTC*, 624 F. Supp. 3d at 465, 469-73.

74. A POSA would be motivated to replace the nebulized solution and nebulizer used in *Faria-Urbina* with a dry powder formulation of treprostinil and DPI known in the art by POSAs and also disclosed in the '793 patent because DPIs are more convenient. Tr. 475:21-476:5.

75. A POSA would also have a reasonable expectation of success in switching from the nebulized Tyvaso formulation to a DPI. Tr. 476:16-477:23. *Faria-Urbina* administered treprostinil by inhalation using the Tyvaso pulsed inhalation device, demonstrating that Tyvaso was safe to use in PH-ILD patients, and improved exercise capacity. Tr. 476:6-8, 476:19-477:3.

A nebulizer and a DPI deliver treprostinil through the same inhaled route. Tr. 476:23-25, 567:13-18. As Dr. Channick testified, a POSA would have no reason to believe that they would not have a similar effect. Tr. 567:21-568:6.

76. In fact, Dr. Nathan testified that even completely different drugs will produce similar results in PH-ILD "no matter how you give them, inhaled, oral, IV, sub-Q, [because] they all dilate the pulmonary vasculature, albeit through different mechanisms." Tr. 831:23-832:15. A POSA would thus have a reasonable expectation of success when replacing the nebulizer used in *Faria-Urbina* with a DPI and dry powder formulation of treprostinil. Tr. 477:13-23.

E. Claims 5, 6, and 9 Are Obvious

77. Asserted claims 5, 6, and 9 are obvious in view of *Faria-Urbina* and the '793 patent in further view of *Saggar 2014*. Tr. 481:22-482:24, 491:14-492:10, 494:8-11, 495:2-19.

78. ***Saggar 2014*,** published in 2014 in the peer-reviewed journal, Thorax, is titled "Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis" with lead author Rajan Saggar. DTX10; Tr. 446:21-447:6. Dr. Nathan testified he was an editor at Thorax and facilitated its publication. Tr. 922:5-15. Dr. Saggar testified that *Saggar 2014* "proved in our minds . . . that this medication was – this molecule, treprostinil, was highly benefi[cial] for PH-ILD" and that it "set the stage for what eventually was the INCREASE study and the eventual FDA approval for Tyvaso for PH-ILD." Tr. 298:8-300:24.

79. *Saggar 2014* diagnosed PH-ILD patients using RHC and HRCT at baseline. DTX10, 2-3; Tr. 921:22-922:4. *Saggar 2014* reports that 15 patients with PH-ILD showed "significant improvements in right heart haemodynamics" and "6MWD improvements following 12 weeks of parenteral treprostinil [(Remodulin)] therapy (mean 59 m; $p<0.001$)"; results similar to those seen in *Faria-Urbina*. DTX10, 4; Tr. 479:3-480:18, 485:20-25, 259:4-263:20.

80. *Saggar 2014* discloses reductions in BNP plasma concentration (DTX10, 5 (Table 4)), a statistically significant reduction in exacerbations of ILD (*id.*, 2, 4 (Table 3)), and a statistically significant improvement in percent predicted FVC (*id.*, 3 (Table 2)). Tr. 480:23-490:8, 491:14-492:10, 262:10-263:20.

81. *Saggar 2014* concludes "[t]his open-label study suggests that gradual initiation and chronic administration of parenteral treprostinil therapy may improve haemodynamics and right heart function without compromising systemic oxygenation in an advanced PH phenotype with RV [(right ventricular)] dysfunction in the setting of PF[,]" and that "[f]uture studies of PH-targeted therapy for PF should focus on patients with PF with the combination of advanced PH and RV dysfunction, as these subjects may have greater capacity for benefit." DTX10, 6-7.

82. Dr. Nathan's claim that no POSA would rely on *Saggar 2014* because it uses IV treprostinil is not credible because it directly contradicts his rationale for relying on the "failed" studies. *See* FOF59. Dr. Nathan's suggestion that *Saggar 2014* is only "hypothesis-generating" is contradicted by UTC's reliance on *Saggar 2014* (*supra* FOF 52, 54) and his characterization of the INCREASE FVC results as merely "hypothesis-generating." FOF132-133.

1. A POSA would be motivated to combine *Faria-Urbina* and the '793 patent with *Saggar 2014* with a reasonable expectation of success

83. A POSA would be motivated to combine *Faria-Urbina* and the '793 patent with *Saggar 2014* with a reasonable expectation of success for claims 5, 6, and 9. Although *Saggar 2014* administered treprostinil parenterally while *Faria-Urbina* and the '793 patent used iTre, all three disclosed similar results with respect to safety and improvements in exercise capacity as evidenced by improvements in 6MWD in PH ILD patients. *See* FOF35, 96; DTX348, 1; DTX10, 1; DTX2, 1; Tr. 391:20-25, 447:18-22, 448:2-10, 454:23-455:1, 463:5-13, 476:19-22, 485:17-25. This is not surprising because all three references used treprostinil, which works as a vasodilator.

Tr. 372:21-374:15, 391:20-392:10, 447:7-448:17, 493:24-294:11, 831:23-832:15.

84. A POSA would be motivated to replace the parenteral administration in *Saggar 2014* with the inhaled route in *Faria-Urbina* and the '793 patent. In fact, *Faria-Urbina* cites to *Saggar 2014* as motivation to treat PH-ILD patients with treprostinil, stating "[i]n accordance with our findings, previous reports using parenteral treprostinil in ILD and PH have shown improvement in six-minute walk test distance and pulmonary hemodynamics without negative impact on systemic oxygen saturation." DTX348, 6; Tr. 394:25-395:14.

85. Beyond the obvious convenience benefits of inhalation compared to IV (Tr. 475:21-476:5, 495:2-19), a POSA would be further motivated to use the inhaled route to minimize the potential for V/Q mismatch. Tr. 391:20-392:10, 397:5-25. V/Q mismatch is a condition where either the ventilation of the lungs or the perfusion of the pulmonary blood vessels is impaired, which can lead to low blood oxygen levels due to mis-matched gas exchange in the lung. Tr. 330:4-23, 372:21-373:16. Although *Saggar 2014* did not observe V/Q mismatch issues, it was believed that systemic delivery of a prostacyclin, like treprostinil, could result in V/Q mismatch. DTX10, 1; Tr. 329:12-330:23. Dr. Waxman addressed the benefits of iTre to avoid V/Q mismatch. DTX140, 8:9-19, 11:10-20; Tr. 373:17-374:15, 382:5-23. He explained that a systemic vasodilator will deliver the drug to all areas of the lung because it vasodilates areas of the lung indiscriminately, but iTre will be delivered only to well-ventilated and perfused areas of the lung and only vasodilate areas where the iTre is delivered. *See* Tr. 372:21-374:15, 392:4-10, 397:5-398:11. Indeed, Drs. Saggar, Tapson, and Waxman confirmed that doctors believed iTre may be more successful in treating PH-ILD because the delivery method would not worsen V/Q mismatch and because the inhaled route made "intuitive sense." *See* Tr. 257:9-24, 372:21-374:15, 392:4-10, 397:5-22, 329:12-330:23.

86. *Agarwal* further provides a POSA with motivation and a reasonable expectation of success in replacing parenteral treprostinil with inhaled because it indicates that "[i]nhaled prostacyclin therapy is delivered directly to well ventilated lung units, preserving V/Q and reducing undesirable alterations in perfusion." DTX161, 8; Tr. 373:17-374:15.

87. Dr. Rajan Saggar testified that he treated PH-ILD patients with Remodulin, IV treprostinil, before 2009. Tr. 255:12-257:1. He testified that after iTre's 2009 approval, it made sense to switch to iTre because it could be used at home as opposed to in an inpatient setting. Tr. 257:9-24. He saw improvements in 6MWD and NT-proBNP levels in PH-ILD patients, attributing these improvements to the fact that treprostinil worked in PH and that it provided similar benefits in Group 3 PH as it did in Group 1 PH. Tr. 257:25-258:17.

88. For these reasons, a POSA would be motivated to seek to achieve the positive results obtained in *Saggar 2014*, but by employing the inhaled route of administration of *Faria-Urbina* and the '793 patent. Additionally, a POSA would have a reasonable expectation of success in combining *Faria-Urbina*, the '793 patent, and *Saggar 2014* to arrive at the limitations in claims 5, 6, and 9 because all three references administered the same molecule, in the same PH-ILD patient population, and observed comparable positive results, consistent with Dr. Nathan's view about vasodilators in general. Tr. 447:7-448:17, 480:16-482:20, 495:2-19, 831:23-832:15.

89. UTC's experts testified that a POSA would not be able to predict how changing both the dosage and administration route for treprostinil would affect the results described in *Saggar 2014* and in view of *Saggar 2014*'s small sample size and lack of control arm. *See* Tr. 857:9-20, 752:16-24. However, the sample size is not disqualifying as prior art and a POSA would not simply disregard relevant clinical reports due to sample size. *See* Tr. 493:3-18. In fact, patient case studies and retrospective reviews are common and important sources of evidence in clinical

practice. Tr. 492:11-23. *Saggar 2014* reports actual clinical results and a POSA would consider them relevant to treating PH-ILD patients with iTre. *See* DTX10; *see also* Tr. 462:20-463:4.

2. Claim 5 is obvious

90. Claim 5 recites "[t]he method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering." JTX1, 50 (cl. 5).

91. In *Saggar 2014*, patients treated with parenteral treprostinil saw their BNP levels fall from 558 pg/ml to 228 pg/ml, a difference of 330 pg/ml, after 12 weeks with a p-value of 0.004. DTX10, 5 (Table 4); Tr. 265:17-266:7. NT-proBNP is a fragment of BNP and both can be measured in circulation. Tr. 481:18-21. BNP and NT-proBNP are both indicators of cardiac function in PH, and as explained by Dr. Channick, they are positively correlated. Tr. 481:18-482:4. Dr. Nathan did not refute this correlation. There is no clear advantage using one biomarker over the other and a POSA would have understood that *Saggar 2014*'s statistically significant reduction of BNP levels correlates with a similar magnitude of reduction in NT-proBNP. Tr. 481:22-482:4. The correlation between BNP and NT-proBNP is confirmed by *Parikh*, which reports a decrease of 630 ng/L in NT-proBNP following administration of iTre in Group 3 PH patients, including PH-ILD patients. DTX51, 3; Tr. 468:13-19.

92. Additionally, Dr. Rajan Saggar testified that his clinic has "seen the same improvements in BNP [and] NT-proBNP" in the PH-ILD patient population with iTre. Tr. 269:25-270:10. Further, because positive results in 6MWD and hemodynamics were observed in PH-ILD patients in both parenteral and inhaled routes of treprostinil administration, a POSA would reasonably expect to achieve a statistically significant reduction in NT-proBNP as well as a reduction of at least 200 pg/ml after 8, 12 or 16 weeks as observed in *Saggar 2014*, when administering via inhalation. *See* Tr. 481:22-482:20, 485:20-25, 495:2-19.

3. Claim 6 is obvious

93. Claim 6 recites "[t]he method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease." JTX1, 50 (cl. 6).

94. Exacerbations present as worsening oxygenation and worsening shortness of breath, which demonstrate respiratory deterioration. *See* Tr. 149:20-150:23, 483:13-20, 396:2-18. If patients are feeling or functioning better, they are not experiencing more exacerbations. Tr. 483:24-484:5, *see also* 187:12-189:15. These improvements are reflected by improvements in 6MWD, functional class, shortness of breath, and quality of life questionnaire scores. Tr. 483:13-486:19. Dr. Waxman also testified that improvement in shortness of breath, as well as an improvement in 6MWD, correspond to a reduction in exacerbations. Tr. 396:2-18.

95. *Faria-Urbina* reported that Group 3 PH patients demonstrated "significant improvement in functional class ($n = 22$, functional class III-IV 82 vs. 59%, $p = 0.041$)." DTX348, 1. Table 2 of *Faria-Urbina* provides the results of the WHO functional class (FC) assessment and confirms the changes were statistically significant. *See id.*, 5. *Faria-Urbina* also disclosed a statistically significant improvement in the 6MWD test. DTX348, 1; DTX505, 3-4. WHO FC determinations and 6MWD performance take into account worsening oxygenation and worsening shortness of breath. Tr. 484:6-485:16, 396:2-18. Accordingly, the statistically significant improvements in FC and 6MWD created a reasonable expectation that a statistically significant reduction in exacerbations would be achieved. Tr. 484:10-21. *Faria-Urbina* further described a decrease in dyspnea (i.e., shortness of breath) in patients treated with iTre, further evidencing a lack of exacerbations of ILD. DTX348, 5 (Table 2); Tr. 484:6-486:19.

96. *Saggar 2014* discloses statistically significant improvements in 6MWD (59 m; $p<0.001$), along with improvements in dyspnea which were measured using the "UCSD SOB"

questionnaire and "SF-36" survey. DTX10, 3-4; Tr. 485:20-486:19. USCD SOB scores improved from 87 to 73.1 with a p-value of 0.002 and SF-36 scores increased from 38 to 33.2 with a p-value of 0.005. *Id.* Like *Faria-Urbina*, these improvements in *Saggar 2014* support a reasonable expectation of success in achieving a statistically significant reduction in an exacerbation of lung disease in PH-ILD patients. Tr. 486:7-19.

97. Because improvements in shortness of breath and improvements in 6MWD were observed with the use of parenteral treprostinil, due to the similarities in patient population, drug, and observed clinical benefits, a POSA would reasonably expect that the inhaled formulation would achieve comparable outcomes. By combining the disclosures of these three references, a POSA would have had a reasonable expectation of success in achieving the limitation of claim 6, rendering the claim obvious. Tr. 494:8-11, 495:2-19.

98. Dr. Nathan's only opinion regarding exacerbations is that "the Saggar paper doesn't mention anything about acute exacerbations. You cannot extrapolate one's exacerbations based on change in six-minute walk distance. The two are totally disconnected." Tr. 863:14-17. Claim 6 does not refer to "acute" exacerbations of ILD and Dr. Nathan did not explain how an "acute" exacerbation is relevant. This testimony is also unsupported by any evidence and is not responsive to Dr. Channick's, Dr. Saggar's, and Dr. Waxman's testimony regarding exacerbations and *Saggar 2014*'s disclosures regarding statistically significant improvements in shortness of breath and 6MWD. *See* Tr. 396:2-18, 482:21-486:19.

4. Claim 9 is obvious

99. Claim 9 recites "[t]he method of claim 1, wherein said administering provides a statistically significant improve[ment] of forced vital capacity (FVC) in the patient after 8 weeks, 12[] weeks, or 16 weeks of the administering." JTX1, 50 (cl. 9).

100. Forced vital capacity (FVC) "refers to the amount of air that can be forcibly exhaled

from the lungs after taking the deepest breath possible, as measured by spirometry." JTX1, 30 (13:4-7); Tr. 486:23-487:3.

101. *Saggar 2014* reports an improvement of 1% predicted FVC in the patient population, as shown in Table 2, reporting a change in percent predicted FVC from 62% at baseline to 63% at 12 weeks. DTX10, 3 (Table 2); Tr. 486:23-488:14. Dr. Rajan Saggar testified that no later than 2010, he developed the expectation that treprostinil would improve FVC in PH-ILD patients, as it improves FVC in some PAH patients. Tr. 259:4-23, 270:19-271:6.

102. The 1% improvement in FVC in *Saggar 2014* is the same change in percent predicted FVC compared to baseline observed in INCREASE and reported in the '327 patent. JTX1, 44 (Table 10); Tr. 488:15-489:3, 489:7-11, 490:4-8, 491:1-9. The percent predicted FVC change at week 8 for the ITT population in INCREASE was 0.77% (week 8) and 1.07% (week 16) as reported in the '327 patent. JTX1, 35 (Table 1). Table 1 also reports that these ~1% improvements in percent predicted FVC corresponded to statistically significant improvements in percent predicted FVC (week 8: p=0.0139; week 16: p=0.0277). *Id.*; Tr. 488:15-489:3, 491:1-5.

103. Further, when discussing a 2021 post-hoc analysis of FVC data from INCREASE by Dr. Nathan, Dr. Wertheim confirmed that while treatment arms in prior studies showed a downward trajectory in FVC data, the treatment arm in the INCREASE study "reversed direction and is . . . going uphill" for FVC. Tr. 792:17-793:8; PDX4, 12; DTX9, 5. This upward slope corresponds to the 1% increase in FVC reported in Example 3 of the '327 patent. JTX1, 35; DTX9, 5. Accordingly, Dr. Nathan's criticism of the 1% increase in FVC in Saggar 2014 as "inconsequential" is misplaced given the same magnitude of results for FVC in INCREASE. *See* Tr. 864:4-14; DTX10, 3 (Table 2).

104. The response rate in terms of improvement in FVC in *Saggar 2014* is also

comparable to INCREASE. Of the 15 patients in *Saggar 2014*, 10 (or 66%) showed improvements in FVC following treprostinil treatment. DTX10, 18; *see also id.* at 3 (Table 2); Tr. 486:20-487:14. In INCREASE, there was significant patient variability in FVC response, and many treated patients actually had worsening FVC compared to baseline (decreases of approximately 15mL at week 16). DTX9, 5 (Figure 1A); Tr. 137:16-20. Therefore, *Saggar 2014* discloses improvements in FVC in terms of % improvement and overall patient response corresponding to the claimed statistically significant improvements in FVC in claim 9.

F. No Secondary Considerations Support the Validity of the '327 Patent

105. Dr. Nathan offered opinions on secondary considerations including unexpected results, failure of others, skepticism, long-felt unmet need, teaching away, industry praise, success, and copying. Tr. 711:23-712:2, 726:9-19. His opinions on secondary considerations are facially insufficient to rebut the strong evidence of obviousness for each of the Asserted Claims.

1. UTC cannot establish a nexus between the Asserted Claims and Tyvaso

106. UTC cannot establish a nexus between the Asserted Claims and Tyvaso or Tyvaso DPI because UTC already admitted to the FDA and USPTO that the prior art '793 patent covered the Tyvaso indication for improving exercise capacity in patients with PH-ILD. FOF31. UTC and Dr. Nathan provided no evidence demonstrating that there was any material difference between the '793 patent and the '327 patent, and more importantly, that any difference between the two can be attributed to the '327 patent and a nexus to secondary considerations.

2. UTC has not established that the claimed invention was unexpected

107. For unexpected results, Dr. Nathan did not compare the Asserted Claims to the closest prior art (e.g., *Faria-Urbina*) and instead compared them to the "failed" studies—none of which even used treprostinil. Tr. 712:9-18; FOF59-66. UTC thus failed to establish that the claimed invention of the '327 patent is unexpected.

108. Additionally, Drs. Tapson, Waxman, and Hill testified that they were not surprised by the results of INCREASE. When asked if the INCREASE results confirmed his prior experience using Tyvaso to treat PH-ILD, Dr. Tapson testified that "it confirmed that the drug worked." Tr. 328:7-15. Dr. Waxman stated that he believed INCREASE would be successful and the results confirmed that he was right. Tr. 414:17-415:6. Dr. Hill testified that he was not surprised because he "expected the results to be positive." Tr. 626:20-627:9.

3. UTC has not established industry skepticism

109. Dr. Nathan says he was skeptical of treating PH-ILD patients with treprostinil based on the "failed studies," but cites to nothing to support alleged skepticism. Tr. 712:21-714:4. Rather, Drs. Rajan Saggar, Waxman, Channick, Hill, and Tapson all testified that they continued to use iTre to treat PH-ILD patients despite the "failed" studies and were aware of doctors' off-label use. FOF59-66, 117-122; Tr. 257:9-17, 333:16-22, 415:15-24, 439:16-440:1; DTX201, 12.

110. Dr. Rajan Saggar testified that he was not surprised that treatment of PH-ILD patients with Tyvaso resulted in significant improvements 6MWD because doctors had already seen such improvements in their own clinical practice. Tr. 269:17-24. He also testified that doctors were not surprised by the improvements in NT-proBNP or in FVC. Tr. 269:25-271:6.

111. When specifically asked about whether other doctors in the field were skeptical of treating PH-ILD patients with iTre, Dr. Waxman stated that "[t]here are definitely some very narrow-minded conservative physicians" who would not "deviate from the guidelines." Tr. 415:19-416:4. But based on the use of Tyvaso by various doctors at various medical centers across the country, it is clear that a large number of doctors were not skeptical. FOF117-122.

4. UTC's additional secondary considerations fail

112. **No Long-felt Unmet Need.** Dr. Nathan testified that there was a long-felt unmet need for improving exercise capacity in PH-ILD patients before INCREASE. Tr. 714:16-715:2.

However, UTC admitted that this need had been met by the '793 patent prior to INCREASE and the '327 patent. DTX7, 62; Tr. 424:12-426:1, 459:24-460:15; DTX28, 6; Tr. 428:14-429:3; 429:16-430:19; 724:8-13. Doctors were already treating PH-ILD patients with iTre, confirming that Tyvaso satisfied the treatment needs of PH-ILD patients prior to April 2020. FOF117-122.

113. **No Teaching Away**. Dr. Nathan also opined that the prior art taught away from the use of iTre to improve the exercise capacity of PH-ILD patients based solely on the "failed" studies that did not use treprostinil. Tr. 717:2-16. Dr. Nathan's arguments fail for the same reasons discussed with respect to unexpected results. FOF59-66, 107-108.

114. **No Industry Praise**. Dr. Nathan states without any support that people reacted with "widespread enthusiasm" and "were pleasantly surprised" with INCREASE's results. Tr. 717:20-718:5. He provided no nexus between these statements and any claimed feature of the '327 patent, and his anecdotes are contradicted by Dr. Waxman's testimony that he believed INCREASE would be successful and the results of INCREASE merely confirmed that he was right. Tr. 414:17-415:6.

115. **No Success**. Dr. Nathan testified about "success," which is not a secondary consideration separate from "commercial success." Tr. 718:6-719:7. No UTC witness offered any evidence of commercial success, let alone commercial success due to the '327 patent.

116. **No Copying**. Dr. Nathan opined Liquidia copied the claimed method of treatment without even specifying which claim elements Liquidia allegedly copied. Tr. 719:9-14. But there is no dispute that Liquidia added the PH-ILD indication to Yutrepia before the November 28, 2023 issue date of the '327 patent. Tr. 57:3-13, 101:25-102:7, 127:15-24. Moreover, his opinion ignores that Yutrepia is a different drug than Tyvaso, as it has an entirely different formulation and is delivered via dry powder as opposed to a nebulizer. Tr. 174:6-15.

V. CLAIMS 1, 5, 6, 9, AND 17 ARE INVALID DUE TO PRIOR SALE

A. The Claimed Invention Was Commercially Sold Prior to April 2019

1. Doctors treated PH-ILD patients with Tyvaso before April 2019

117. Tyvaso was approved to treat PAH in 2009 and approved to treat PH-ILD in March 2021. Tr. 597:10-15, 33:7-10; DTX357, 2. Tyvaso was the only iTre therapy on the market prior to the approval of Tyvaso DPI. Tr. 369:9-13, 384:11-13, 455:2-19, 464:13-16.

118. Off-label use of drugs by doctors is permitted by the FDA and may ultimately lead to the approval of the drug such that it becomes on-label for the indication. Tr. 597:21-598:6.

119. As early as 2009, and prior to April 2019, Dr. Hill prescribed Tyvaso off-label to several dozen PH-ILD patients. Tr. 595:18-597:20. These patients exhibited improvements in exercise capacity, including improvements in 6MWD. Tr. 599:5-600:10.

120. Drs. Waxman, Tapson, Rajan Saggar, and Channick prescribed Tyvaso off-label to PH-ILD patients, beginning in 2009. Tr. 372:4-376:15, 381:19-386:18, 414:3-414:5, 415:7-416:4, 328:25-330:3, 331:25-333:22, 255:12-258:2, 264:19-265:1, 267:6-268:19, 439:13-440:1. These patients exhibited improvements in exercise capacity, including in 6MWD, and other improvements, including in NT-proBNP. Tr. 386:9-18, 331:8-24, 257:25-259:24, 440:2-10.

121. These five doctors were all capable of diagnosing PH-ILD, and indeed diagnosed their patients as having PH-ILD when they treated them with Tyvaso prior to April 2019. FOF3, 22; Tr. 132:9-15, 325:5-23, 617:2-25, 722:18-724:1. Drs. Waxman and Tapson were members of the INCREASE steering committee, which UTC used to obtain approval of the PH-ILD indication for Tyvaso. FOF51; DTX401, 4; Tr. 33:7-20, 398:12-401:1, 325:5-19, 125:19-127:7.

122. Drs. Hill, Waxman, Tapson, Saggar, and Channick all prescribed Tyvaso off-label using the following dosing—3 breaths 4 times a day, titrating up to a maximum dose of 9 to 12 breaths 4 times a day as tolerated, where each breath consists of 6 micrograms of iTre. Tr. 286:4-

22, 334:4-336:8, 375:15-379:20, 381:21-384:5, 439:13-440:14, 592:9-593:13, 596:4-10. This dosing is consistent with the dosing in the 2009 Tyvaso label (Tr. 334:4-336:8, 375:15-378:18; DTX357, 2), the 2021 Tyvaso label (Tr. 338:3-341:2; DTX360, 1), and the dosing used in INCREASE (Tr. 338:3-341:2, 403:2-406:1; DTX363, 3). The dosing in INCREASE was based on the experience doctors had in treating PH-ILD patients with Tyvaso. Tr. 401:11-406:1.

2. Tyvaso was prescribed and sold to PH-ILD patients to improve exercise capacity prior to April 2019

123. UTC does not dispute that Tyvaso was on sale as of 2009. Tr. 891:13-15. UTC sells Tyvaso to specialty pharmacies that sell Tyvaso to individual patients. Tr. 642:7-15. UTC sells Tyvaso with an FDA-approved label and package insert. Tr. 642:16-18.

124. Dr. Hill explained that doctors prescribed Tyvaso for PH-ILD patients via an insurer's form with "a checkbox for Group 1 pulmonary hypertension or pulmonary arterial hypertension and also checkboxes for comorbidities like ILD," and they would "check the PAH box generally because of the hemodynamic profile … [and] would also check the ILD box because the patient had ILD[.]" Tr. 600:17-601:11. Those prescriptions were denied by insurers, especially soon after the 2009 approval of Tyvaso for PAH, but doctors learned how to convince insurers to cover the cost of Tyvaso for PH-ILD patients, for example by characterizing their patients' PH-ILD as having "out of proportion" PH. Tr. 267:6-268:24, 381:1-20. Dr. Hill would submit appeal letters to the insurers' denial of the Tyvaso prescription for PH-ILD, which would lead to a face-to-face peer review with doctors from the insurers where Dr. Hill would ultimately obtain approval by convincing them that there was reason to expect benefit from the use of Tyvaso in PH-ILD patients. Tr. 603:25-604:23.

125. Doctors and insurers recognized that the prescription of Tyvaso prior to April 2019 was for an off-label indication of treating PH-ILD patients. Tr. 617:2-618:4. Insurers would not

have been justified in denying coverage for a pure PAH patient without any PH-ILD. Tr. 617:2-618:4. Dr. Nathan acknowledged that the doctors' prescriptions of Tyvaso for PH-ILD patients were rejected "even when they checked the box for diagnosing with PAH," evidencing that the prescription was not for an approved use. Tr. 892:15-893:18.

126. All five doctors obtained insurance coverage for Tyvaso they prescribed to PH-ILD patients. Dr. Saggar explained that he also convinced insurers to cover Tyvaso for his PH-ILD patients within about six months after Tyvaso's approval. Tr. 267:6-268:24. Dr. Waxman described his patients' PH-ILD as "out of proportion" to secure insurance coverage for Tyvaso. Tr. 381:1-20, 414:2-8. Dr. Tapson's nurses, at Duke and Cedars Sinai, facilitated and obtained insurance coverage for the Tyvaso prescribed to his PH-ILD patients. Tr. 336:10-337:21.

127. UTC's CEO, Dr. Rothblatt, confirmed this in public statements during UTC's Q1 2018 Earnings Call, stating that "through the kindness and generosity of certain payers around the country who have gone ahead and upon the initiative of their doctors, were able to enable some WHO Group III patients to benefit" from Tyvaso. FOF57; DTX3, 10; Tr. 421:15-422:2, 606:12-610:9. Dr. Rothblatt specifically referenced PH-ILD patients. DTX3, 10; Tr. 609:14-610:9.

128. The doctors' treatment of PH-ILD patients with Tyvaso was not experimental nor prescribed as part of a clinical trial. DTX3, 10; Tr. 336:10-25, 382:5-386:8, 387:8-388:14, 468:20-470:4. The Tyvaso that the doctors prescribed was not given out for free. Tr. 336:10-25.

3. Off-label sale and treatment of PH-ILD with Tyvaso is corroborated by peer-reviewed publications

129. *Faria-Urbina* corroborates Dr. Waxman's successful off-label treatment of PH-ILD patients with Tyvaso prior to April 2019. DTX348, 1-2; Tr. 387:8-389:6, 612:20-613:19; FOF19-27, 34-35. *Parikh* corroborates Dr. Tapson's off-label treatment of PH-ILD patients with Tyvaso prior to April 2019. DTX51, 1-3; Tr. 341:7-346:16, 612:20-613:19, 700:18-704:6; FOF38,

42-45. Tyvaso is not free, and the patients were not in a sponsored clinical trial, further confirming Tyvaso was sold to PH-ILD patients. FOF128. Both articles were peer-reviewed, meaning reviewers agreed with the articles' disclosure of successfully treating PH-ILD patients with Tyvaso as of the date of each paper. Tr. 382:5-386:8, 336:10-18, 620:1-620:12, 921:20-922:15. Finally, an article authored by Dr. Nathan acknowledges widespread off-label use of PAH therapies for treatment of PH-ILD. DTX201, 12; Tr. 613:23-616:21.

B. The Claimed Invention Was Ready for Patenting

1. Claim 1 was reduced to practice

130. Doctors treated PH-ILD patients with Tyvaso to improve exercise capacity according to dosing consistent with claim 1. FOF117-122. Doctors confirmed the method of treating PH-ILD patients with Tyvaso worked for its intended purpose by observing improvements in exercise capacity, and therefore claim 1 was reduced to practice prior to April 2019. *Id.*; Tr. 618:24-619:17, 619:18-25.

2. *Faria-Urbina* enabled a POSA to practice claims 1 and 17

131. *Faria-Urbina* discloses (1) treating PH-ILD patients, (2) with iTre, (3) using dosing consistent with INCREASE and claim 1, and (4) improvements in exercise capacity. FOF21-27, 67. A POSA following the Tyvaso dosing in *Faria-Urbina* was enabled to practice the method of claim 1 and achieve the result of improving exercise capacity, as well as increasing 6MWD by at least 10m after 8 weeks of administration per claim 17. Tr. 620:20-622:25. Claims 1 and 17 were reduced to practice no later than the 2018 publication date of *Faria-Urbina*. *Id.*

3. Hypothesis-generating results demonstrate ready for patenting

132. As Dr. Hill explained, even hypothesis-generating results confirm the '327 patent invention was ready for patenting, as they indicate that the treatment produced positive results that lay the foundation for further research, like Dr. Waxman's work and data led directly to

INCREASE. Tr. 627:10-630:2, 398:12-400:2017, 234:21-236:18, 312:2-319:4; DTX3, 10 (stating that UTC ran INCREASE based on "data, some of which has been presented in posters and maybe even publications" that Tyvaso "works even better in [the Group III] indication than in the Group I indication in terms of … the exercise ability that they saw in their patients").

133. Dr. Nathan characterized the FVC results from INCREASE as "hypothesis generating" and UTC obtained claim 9 based on those results, confirming that hypothesis-generating results are sufficient to establish ready for patenting. DTX9, 9; Tr. 628:36:1-629:86.

4. The prior sale of Tyvaso inherently anticipates claims 5, 6, and 9

134. The NEJM Paper discloses the dosing of INCREASE, which is the same dosing doctors used in PH-ILD patients prior to 2019. DTX363, 1; FOF122. The NEJM Paper discloses improvements in NT-proBNP, statistically significant reductions in exacerbations of ILD, and statistically significant improvements in FVC. DTX363, 7-8, 36; Tr. 633:1-22. Because those improvements satisfy the requirements of claims 5, 6, and 9, these limitations are inherently met by the doctors' off-label treatment of PH-ILD patients with Tyvaso using the same dosing as in the NEJM Paper. Tr. 630:31-635:1; FOF117-29.

VI. CLAIMS 1, 5, 6, 9, AND 17 ARE INHERENTLY ANTICIPATED

A. Claims Do Not Require "Virtually All" to Achieve the Claimed Results

135. Claim 1 recites "[a] method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease …" JTX1, 50. Under the Court's construction of "a" or "the," the experts agree the claims do not require that "virtually all" patients achieve the recited outcomes, but rather only "one or more" patients must achieve the recited outcomes. D.I. 155; Tr. 137:5-10, 511:9-21, 632:3-25, 924:21-925:1.

136. In clinical practice, methods of treatment do not benefit "virtually all" patients. Tr. 137:21-138:5, 511:22-24, 671:15-672:15. Indeed, not all patients in the INCREASE study

achieved the recited outcomes. Tr. 511:25-512:2, 137:8-20, 822:13-22. Results from clinical trials such as INCREASE could never be perfectly re-created even if the clinical trial were re-run exactly. Tr. 136:16-137:1, 542:18-543:12, 566:20-567:1.

B. The 2017 INCREASE Protocol (DTX8)

137. The 2017 INCREASE Protocol, submitted to clincialtrials.gov on February 9, 2017 and posted online on February 10, 2017, is a public disclosure of the protocol used in INCREASE (NCT02630316). DTX8, 8; Tr. 495:24-496:15. Other than small differences in the inclusion criteria, the 2017 Protocol describes the design of INCREASE as it was conducted. Tr. 498:17-499:13, 496:23-497:23.

138. INCREASE's results were reported in the NEJM Paper detailing the results of INCREASE. DTX363; *see also* Tr. 406:22-407:8, 588:23-589:1; FOF55-56.

139. The results of INCREASE led to the claims of the '327 patent. Tr. 134:14-20, 232:14-16, 234:21-235:13, 504:2-17, 910:9-12. Based on the Court's construction of "a" or "the," the claims at issue require only that one single patient (or more) achieve the claimed results in order for the claim to be practiced. Tr. 137:5-10, 511:9-21, 632:3-25. Therefore, the 2017 Protocol inherently anticipates the '327 patent claims so long as the claimed results were achieved in at least one patient in INCREASE.

1. The 2017 Protocol described the design and purpose of INCREASE

140. The 2017 Protocol provides details of the protocol used in INCREASE. Tr. 498:17-499:13. The 2017 Protocol describes a 16-week, multicenter randomized double blinded placebo-controlled trial of 314 patients to "evaluate the safety and efficacy of iTre in subjects with pre-capillary pulmonary hypertension (PH) associated with interstitial lung disease (ILD) including combined pulmonary fibrosis and emphysema (CPFE)." DTX8, 9; Tr. 496:23-497:6.

141. The 2017 Protocol further describes how INCREASE would examine

administering iTre at the same dose as recited by claim 1, administering "[a]ctive [t]reprostinil for inhalation solution (0.6 mg/mL) delivered via an ultrasonic nebulizer which emits a dose of approximately 6 mcg per breath. Inhaled four times daily and titrated up to a maximum of 12 breaths four times daily." DTX8, 10; Tr. 497:17-498:16.

142. The 2017 Protocol was prepared with input and guidance from the INCREASE Steering Committee, including its chairman, Dr. Waxman. Tr. 401:11-21. Named inventors Leigh Peterson and Peter Smith were not involved in developing the INCREASE Study and joined the program after the 2017 Protocol was finalized and CQ Deng did not offer testimony as to his role. Tr. 244:8-245:5, 240:20-241:5; FOF48.

2. The 2017 Protocol defines the same endpoints as the INCREASE study

143. The 2017 Protocol discloses all the endpoints of INCREASE (as well as the asserted claims of the '327 patent). Tr. 505:1-9, 506:1-25, 910:25-911:6; *compare* DTX8, 9-10, *with* JTX1, 50 (all claims).

144. The 2017 Protocol's primary outcome measured 6MWD from baseline to week 16. Tr. 506:13-23. This was the same primary outcome measured in the INCREASE study, and reflects an improvement in exercise capacity as recited by claim 1. DTX363, 3; Tr. 506:21-25. It also reflects the 6MWD outcome measure recited by claim 17. Tr. 507:1-4.

145. The 2017 Protocol's secondary outcome measures included: changes in plasma NT-proBNP levels from baseline to week 16, and changes in FVC from baseline to week 16, as recited by claims 5, 6, and 9, respectively. DTX8, 9-10. INCREASE measured the changes in plasma NT-proBNP levels from baseline to week 16, as recited by claim 5. Tr. 507:5-508:8; DTX363, 4-5, 8. INCREASE also measured reductions in exacerbations of ILD, as recited by claim 6. Tr. 508:9-509:4; DTX363, 4-5, 8. INCREASE also measured changes in FVC from baseline to week 16, as recited by claim 9. Tr. 509:5-510:9; DTX363, 4-5, 8.

3. The PH-ILD population of the 2017 Protocol is included in the INCREASE study and the PH-ILD population of the claims

146. The patient population defined in the 2017 Protocol was virtually the same as, and was included within, the patient population that was actually recruited into INCREASE. Tr. 498:17-23, 502:16-503:15. This is shown by the similar inclusion criteria of the 2017 Protocol and INCREASE. Tr. 498:24-499:13; DTX8, 12-13; DTX363, 2-3.

147. The 2017 Protocol inclusion criteria required: "a right heart catheterization (RHC) within 1 year prior to randomization with the following documented parameters: 1. Pulmonary vascular resistance (PVR) ≥ (greater than or equal to) 4 Wood Units (WU) and … 3. [a] mean pulmonary arterial pressure (mPAP) of ≥ (greater than or equal to) 30 mmHg." DTX8, 12.

148. The primary difference with the 2017 Protocol was that INCREASE broadened the types of ILD that could be studied, and lowered PVR requirements to include patients with somewhat milder PH. Tr. 499:14-500:15. The inclusion criteria for INCREASE as reported in the NEJM Paper required PVR of >3 WU and mPAP of ≥25 mm Hg. DTX363 at 2. '327 Patent Table 7 shows the actual PH-ILD patient population participating in INCREASE had an mPAP of up to 74 mmHg and PVR values of up to 18.05. Tr. 907:1-908:1; JTX1, 41-42. And as shown in NEJM Paper Table S2, the patients actually enrolled in INCREASE had mean PVR values ranging from about 6.0 to 6.4 and mean mPAP pressures ranging from about 36 to 37 mmHg. Tr. 502:16-503:18; DTX363, 31. The 2017 Protocol was not meaningfully different from INCREASE in terms of PCWP: the 2017 Protocol used PCWP >15 mmHg as an exclusion criteria, while INCREASE used PCWP ≤15 mmHg as an inclusion criteria. *Compare* DTX8, 13, *with* DTX363, 16. Dr. Channick also testified that parameters of "carbon monoxide DLCO" and 70% maximum FVC would not provide any reason that the 2017 Protocol would not necessarily and inevitably anticipate. Tr. 530:3-533:22, 537:24-538:23. The actual patient population enrolled in the study

reflects UTC's desired population, confirmed by Dr. Tapson, of PH-ILD patients with severe, not mild PH. Tr. 326:6-327:14. INCREASE included 326 patients under its broadened inclusion criteria, 12 more than the 314 estimated in the 2017 Protocol. DTX8, 9; Tr. 496:23-497:16.

149. Even with slightly different inclusion criteria, all patients defined in the 2017 Protocol would have been included in the final INCREASE study, as demonstrated by the NEJM Paper and Table 7 of the patent. Tr. 501:23-25, 502:16-503:12; JTX1, 41-42; DTX363, 31.

4. The 2017 Protocol defines the same dosing as INCREASE

150. The 2017 Protocol literally describes claim 1's requirement of "administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath." JTX1, 50 (cl. 1).

151. Specifically, the 2017 Protocol describes the administration of iTre in INCREASE as "via an ultrasonic nebulizer … which emits a dose of approximately 6 mcg per breath…. Inhaled four times daily and titrated up to a maximum of 12 breaths four times daily." Tr. 525:18-526:16; DTX8, 10. This literally discloses the "at least 15 micrograms" of treprostinil at "6 micrograms per breath" limitations of claim 1. Tr. 528:6-25; *see* DTX8, 10; JTX1, 50 (cl. 1).

152. Dr. Nathan testified that the dosing of the 2017 Protocol did not specify the starting dose of three breaths that was actually used in INCREASE. Tr. 817:24-818:4. However, Dr. Nathan acknowledged that in 2017, doctors understood from the 2009 Tyvaso label that "[t]herapy should begin with three breaths of Tyvaso." DTX357, 3 (2009 Tyvaso label); Tr. 920:11-23; FOF36, 122. Dr. Hill, who was an investigator in INCREASE, further testified that prior to April 2020, doctors—including Dr. Waxman, who helped design the 2017 Protocol—dosed PH-ILD patients with Tyvaso according to the 2009 Tyvaso label. Tr. 588:12-589:1, 592:25-593:13; *see*

also id. at 401:11-21. Dr. Hill also testified that doctors understand that an instruction to titrate up to a maximum of 12 breaths does not mean that 12 breaths needs to be reached, but instead the patient would be titrated up to a tolerated number of breaths, including 9 breaths, and would be maintained at that 9 breath dosage if they couldn't tolerate more. Tr. 593:14-594:14.

C. The 2017 Protocol Inherently Anticipates Claims 1, 5, 6, 9, and 17

153. The iTre dosing in the 2017 Protocol reflects the dosing, PH-ILD patient population, and improvement in exercise capacity evaluated by INCREASE and recited in claim 1. *See supra*, FOF137-152.

154. The 2017 Protocol describes "a method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease." Tr. 504:15-25.

155. The results of INCREASE, reported in the NEJM Paper, demonstrate that, if the described PH-ILD patients are treated with the method in the 2017 Protocol, at least one such PH-ILD patient would necessarily and inevitably experience the improvement in exercise capacity of **claim 1**, evidenced by an increase in 6MWD. Tr. 505:10-19, 506:13-507:4, 564:21-565:2; DTX363, 8, 24-26, 29; Tr. 153:20-23. Notably, INCREASE did not lead to the recited improvement in exercise capacity for "virtually all" of the treated patients in the study. Tr. 511:25-512:2, 137:5-138:5. Dr. Nathan testified that not all of the patients in INCREASE improved their exercise capacity as required by claim 1. Tr. 822:13-22. INCREASE which led to the '327 patent was the confirmation in a Phase 3 trial of the natural result that flowed from treating PH-ILD patients with iTre. Tr. 328:7-24, 414:17-22, 626:20-627:9.

156. The results of INCREASE, reported in the NEJM Paper, demonstrate that if the described PH-ILD patients are treated with the method in the 2017 Protocol, at least one such PH-ILD patient would necessarily and inevitably experience a reduction of a plasma concentration of NT-proBNP of at least 200 pg/ml in the patient after 8 weeks, 12 weeks, or 16 weeks of

administering as recited in **claim 5**. Tr. 507:11-508:8, 633:7-10, 633:23-634:9; DTX363, 8 (Table 2); *see also* Tr. 142:13-17.

157. The results of INCREASE, reported in the NEJM Paper, demonstrate that if the described PH-ILD patients are treated with the method in the 2017 Protocol, at least one such PH-ILD patient would necessarily and inevitably experience a statistically significant reduction in at least one exacerbation of the interstitial lung disease as recited in **claim 6**. Tr. 508:19-509:4, 633:11-15, 634:10-17; DTX363, 7; DTX8, 10; *see also* Tr. 142:13-17.

158. The results of INCREASE, reported in the NEJM Paper, demonstrate that if the described PH-ILD patients are treated with the method in the 2017 Protocol, at least one such PH-ILD patient would necessarily and inevitably experience a statistically significant improvement in FVC after 8 weeks, 12 weeks or 16 weeks as recited in **claim 9**. Tr. 509:11-510:9, 633:17-22, 634:18-635:1; DTX8, 11; DTX363, 36 (Table S6); *see also* Tr. 142:13-17.

159. The results of INCREASE, reported in the NEJM Paper, demonstrate that if the described PH-ILD patients are treated with the method described in the 2017 Protocol, at least one such PH-ILD patient would necessarily and inevitably experience an increase in 6MWD of at least 10 meters after 8 weeks as recited in **claim 17**. Tr. 506:1-507:4; DTX8, 10; DTX363, 8 (Table 2), 24 (Figure S1); *see also* Tr. 142:13-17.

VII. ASSERTED CLAIM 9 IS INVALID UNDER § 112

160. Claim 9 depends from claim 1 and requires "a statistically significant improve[ment] of forced vital capacity (FVC) in the patient after 8 weeks, 12[] weeks or 16 weeks." JTX1, cl. 9. Claim 10 depends from claim 9 and additionally requires an improvement in FVC by "at least 20 ml after 8 weeks, 12 weeks, or 16 weeks." *Id.*, cl. 10.

A. FVC Encompasses Both Absolute and Percent Predicted FVC

161. Given the disclosures in the '327 patent and the state of the art, a POSA would

understand that "forced vital capacity (FVC)" in claim 9 encompasses both absolute and percent predicted FVC, which are two distinct types of potential FVC measurements. Tr. 516:8-14; D.I. 380, 28:24-29:14; JTX1, 35-36, 44 (Tables 1-3, 10); Tr. 770:2-7. Absolute FVC is the volume of air a patient can force out of their lungs and is expressed in milliliters (ml). Tr. 514:20-22, 770:8-18. Percent predicted FVC normalizes the FVC value based on characteristics of height, age, sex, etc. Tr. 514:23-515:1, 770:8-18.

162. Claim 9 says nothing about FVC being limited to only one of absolute or percent predicted FVC, and dependent claim 10 specifies absolute FVC with its "20 mL" limitation. JTX1, cl. 9; Tr. 515:20-516:14. The specification also expresses no preference for either FVC measure. The Summary section describes both absolute and percent predicted FVC measures. JTX1, 2:4-52; Tr. 580:17-582:6. Example 1 discusses "FVC suggestive data," describing both absolute and percent predicted FVC measures. JTX1, 22:50-65. Example 2 further demonstrates the lack of preference: "[c]hange in baseline to Week 24 of treatment in FVC (*absolute or percent predicted*) as primary efficacy endpoint will be assessed." JTX1, 25:53-55 (emphasis added). Tables 1-3 and 10 report both FVC measures. JTX1, 35-36, 44; Tr. 515:2-15, 516:15-18, 518:15-20, 520:7-521:22, 794:21-795:3, 797:2-799:5. These Tables also show that "the same breath coming out of the patient" may lead to different statistical results, depending on which FVC measure is used. JTX1, 35-36, 44; Tr. 807:21-809:2.

163. Dr. Wertheim argued a POSA would find percent predicted FVC more valuable than absolute FVC because it "communicates ... the clinical context," but Dr. Nathan testified the opposite: "absolute [FVC] is more valid ... because you're measuring the patient against themselves at baseline and not the percent predicted." Tr. 801:7-801:18, 926:5-927:22. Dr. Wertheim ultimately admitted that, in claim 9, either absolute or percent predicted FVC would

satisfy this claim's FVC requirement, and the full scope of claim 9 covers either absolute or percent predicted FVC, meaning the full scope covers both. Tr. 793:25-794:4, 811:4-8.

B. The Claimed PH-ILD Patient Population Encompasses the ITT Population

164. A POSA would understand that the claimed "patient having pulmonary hypertension associated with interstitial lung disease" encompasses the entire ITT population in INCREASE. Tr. 513:13-514:6, 515:2-19, 516:19-25, 518:15-520:15, 521:11-22, 807:10-20.

165. Claim 9 depends from claim 1 and neither specify which type of PH-ILD patient will receive treatment. JTX1, cls. 1, 9; Tr. 71:10-72:25, 130:8-134:13, 171:18-172:11.

166. Tables 1-3 and 10 provide FVC measurements. JTX1, 35-36, 44. Tables 1 and 10 describe all patients treated in INCREASE (i.e., ITT population). JTX1, 35, 44; Tr. 513:13-514:6, 515:2-19, 516:19-25, 520:10-15, 521:11-22, 807:3-20. Table 2 shows FVC data from a subpopulation of Table 1—patients with IIP. JTX1, 35; Tr. 518:15-519:13, 578:25-579:25, 797:2-13. And Table 3 is a "subgroup of the subgroup" of patients shown in Table 2—patients with IPF. JTX1, 36; Tr. 519:14-520:6, 580:1-3, 797:23-798:6, 807:3-9. A POSA would consult the information contained in Tables 1 and 10 for information pertaining to the full scope of claim 9 as these tables contain data for the full patient cohort, while Tables 2 and 3 are only subgroups and not the full scope. JTX1, 35, 36; Tr. 521:6-22, 807:3-12.

167. Given claim 9 depends from claim 1, a POSA would understand claim 9 covers statistically significant improvements in FVC for the entire claimed PH-ILD (i.e., ITT) population.

C. A POSA Would Not Find the Full Scope of Claim 9 Adequately Described

168. No data in Tables 1-3 or 10 demonstrate the full scope of the claimed PH-ILD population experienced statistically significant improvements in both absolute and percent predicted FVC following administration of iTre. JTX1, 35-36, 44; Tr. 514:7-13. Tables 1-3 and 10 do not provide any data for 12 weeks after administration. JTX1, 35-36, 44.

169. Tables 1 and 10 describe the full scope of claim 9's PH-ILD patient population, but do not demonstrate any statistically significant improvements in absolute FVC. JTX1, 35, 44; Tr. 517:1-518:14, 520:16-19. The p-values reported in Tables 1 and 10 at weeks 8 and 16 for absolute FVC are 0.3453 and 0.2106, respectively, which are greater than 0.05 and indisputably not statistically significant. JTX1, 35, 44; Tr. 517:1-518:14, 520:16-19, 576:22-577:8, 799:14-19, 808:13-20. Percent predicted FVC values in Tables 1 and 10 were statistically significant at weeks 8 and 16, but this represents only a portion of the full FVC scope. JTX1, 35, 44; Tr. 518:11-14. The inventors did not possess what they claimed: a statistically significant increase in absolute FVC in PH-ILD patients treated according to claim 1. Tr. 514:7-13.

170. Tables 2 and 3 do not cure these deficiencies because they are limited to PH-ILD subgroups (IIP and IPF) for week 8 and 16 visits, and claim 9 is directed to the entire PH-ILD patient population disclosed in the specification at weeks 8, 12, or 16. JTX1, 35, 36; Tr. 797:2-798:20. While Table 2 provides a statistically significant result in absolute FVC for IIP patients at week 16 only, this is not the ITT population of claim 9, and represents, at most, only half the claimed PH-ILD patients. JTX1, 35; Tr. 518:15-519:10, 578:25-579:25, 797:2-13.

171. Similarly, Table 3 provides that the absolute FVC for the IPF subgroup at week 16 was statistically significant (p-value of 0.0108). JTX1, 35; Tr. 580:1-10. However, this represents less than a third of the scope of PH-ILD patients in claim 9. Tr. 519:14-520:6.

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